

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
22 February 2001 (22.02.2001)

PCT

(10) International Publication Number
WO 01/13102 A1(51) International Patent Classification⁷: G01N 27/327,
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(21) International Application Number: PCT/GB00/03054

(22) International Filing Date: 8 August 2000 (08.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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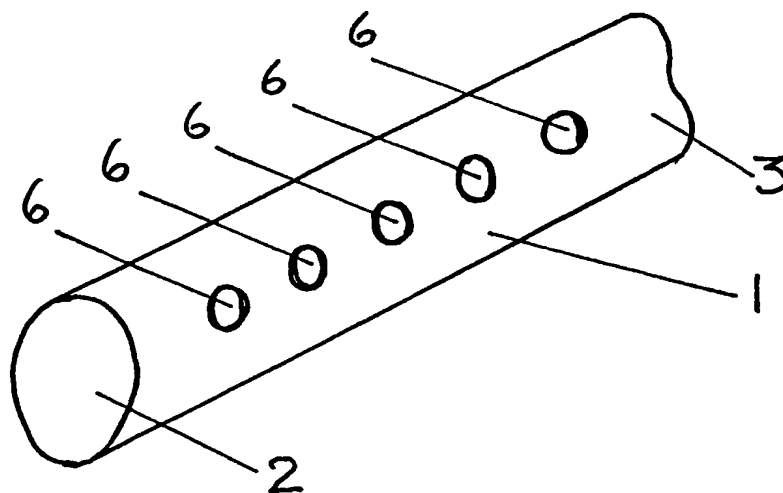
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Worsley, Manchester M28 4QA (GB).(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SENSOR DEVICES AND ANALYTICAL METHODS FOR THEIR USE



(57) Abstract: Sensor devices with an enzyme retained in one or more cavities formed in active electrode core, having the cavities along the length of the electrode core so that the enzyme faces laterally instead of towards or at the mechanically vulnerable tip. This improves effectiveness and ease of use. They are especially wire electrodes, preferably of platinum, and the cavities may be formed as holes cut in the covering insulation on a wire or cut deeper and into the electrode core material itself, e.g. by laser-drilling. One preferred cavity form is a lateral slot and another is a "tunnel" hole cut through the core to expose enzyme at both ends, and the enzyme can be covered by a porous or perm-selective membrane. The sensors are useful for measuring of analytes amperometrically in biological media, and especially glucose on blood/serum using glucose oxidase as the enzyme.

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(19) World Intellectual Property Organization
International Bureau



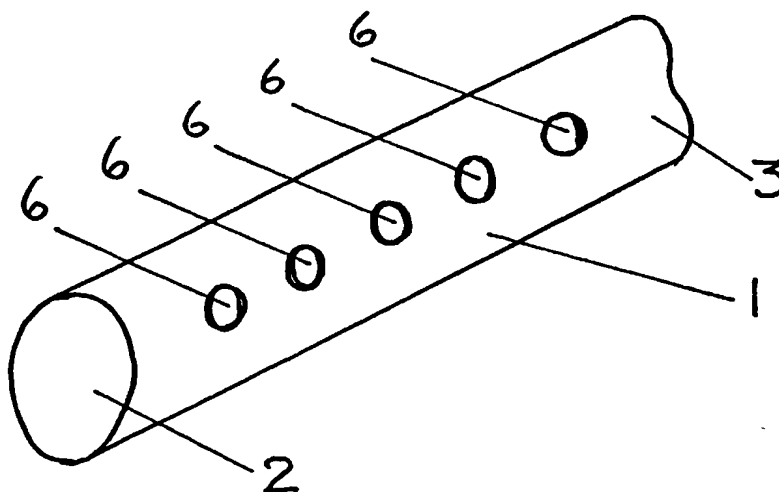
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- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
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— With international search report.
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SENSOR DEVICES AND ANALYTICAL METHODS FOR THEIR USE.

This invention relates to improved sensor devices and methods for their analytical use, and more particularly to improved forms of enzyme electrodes.

5 There is an increasing need for procedures and devices which can enable the presence and amount of particular components (analytes) in biological media to be measured without having to rely on taking samples periodically and taking them away to be analysed in a laboratory. Such old
10 "sampling" procedures - though usually accurate - are too slow and involve a significant delay in obtaining the result of the measurement, and in many circumstances this delay can be inconvenient and even dangerous to a subject.

 Instead, it is very desirable to have a continuing
15 monitoring procedure can be carried and used to detect changes as near as possible to the moment at which they occur, especially if the changes are abrupt or fluctuating. This is important because conditions in some biological environments, and especially conditions in vivo, can change
20 unexpectedly and quickly -- and some measurements may be useful as indications of progress or even critically important as vital indication or warning of a need for speedy remedial action.

 Especial interest exists in measuring glucose levels in
25 body tissue or body fluids, as glucose is vital for life and its level is greatly affected by some conditions, for example diabetes mellitus. Other analytes, e.g. drugs and metabolic products, are also of comparable interest.

 For a continuous monitoring system, it is very
30 desirable to implant a sensor device in the biological environment or medium, and especially an in vivo environment, so that parameters of a living environment or process can be made. Indeed, the only routinely usable monitoring system for an ambulatory diabetic would be either
35 a portable or an in vivo device.

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A variety of such implant devices have been proposed, but their success and applicability vary considerably. The devices or approaches suggested hitherto could, in principle, eventually allow for reliable monitoring but they suffer from various deficiencies and are not entirely satisfactory. For example, many can lack sensitivity or specificity and, as results are often plotted as graphs, show difficulty in making true measurements independently of base-line or response slope variability in such graphs. Further, in some cases it can be impossible to arrive at meaningful in vivo data without in vivo calibration, particularly in a tissue matrix, and the implant may even provoke tissue rejection.

It has been proposed to meet some of these needs by inserting into living tissue a sensor device substantially in the form of a needle incorporating a sensor electrode. Such an electrode may be used in conjunction with a reference electrode - which may be combined with the sensing electrode in the sensor device or may be used separately from it, for example on the skin of the subject.

Such sensors commonly use an active sensor electrode in conjunction with an enzyme, so that the sensor device can be made to respond to selected analyte species which would in themselves be inactive at the electrode and so would not be detected by it, e.g. glucose oxidase for measuring glucose content. Likewise, various forms of coating materials or membranes (permeable or permselective) are commonly proposed for regulating the access of analyte to the active electrode or reducing interference from other compounds which could interfere with the effectiveness of the measurements of the desired analyte if they reach the electrode surface.

It has been proposed to use fine wires of an appropriate electrode material, bare or appropriately coated, compatible with the environment in which it is to be inserted. Even the smallest sensor devices proposed so far

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have been found to have several difficulties in use, which it would be very desirable to overcome, for example:-

(1) Present devices can be too large for easy use (e.g. they may cause undue discomfort to the subject) so greater
5 miniaturisation is desirable to reduce the effect the implanted sensor may have on the subject's behaviour and tolerance of the implant. Also it is desirable to achieve a size of device which allows for an adequate balance between rigidity and flexibility, so that the device is more durable
10 and more easily implanted.

(2) Many known devices employing any coating on the electrode surface - enzyme, membrane, etc. - suffer from difficulties in the stage of insertion into the subject tissue. The enzyme and/or membrane material can be
15 destroyed or displaced using the insertion, to the detriment of the sensor device's effectiveness in subsequent use. This is almost unavoidable, as the friction between the tissue and the coating on the sensor device can be considerable --especially as the coating material is usually
20 of a very delicate nature.

(3) It is very difficult to make sensor devices which are both small and effective. The fabrication of very small devices can be difficult, and it is also difficult to achieve the formation of reliable and stable coatings on
25 them. For example, some devices proposed so far are little more than wires having an exposed tip which is the enzyme/membrane system -- and it is especially difficult to coat the tip of a thin wire.

For use, it has been proposed to implant electrodes in
30 tissue through a cannula to avoid undesirable damage during the insertion stage, but this still involves some friction within the cannula. Attempts to enclose the whole device in a sheath of protective material which may contribute to the electrical function of the sensor electrode (e.g. a
35 reference electrode) or as a strengthening or stiffening aid

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have been proposed, but these tend to increase the size of the device and complicate provision of the necessary degree of exposure of enzyme-coated electrode for effective measuring activity.

5 The aim of our invention is to reduce the size of sensor implants to the practicable minimum compatible with robust mechanical integrity, and also to provide a compliant insert that reduces patient discomfort beyond that achieved to date.

10 We have now found that miniaturised devices which can overcome such disadvantages can be achieved by modifying the shape of the sensor device (especially one incorporating a wire electrode) by forming cavities in the otherwise smooth material of the sensor device and using these cavities to
15 retain the enzyme. In this way, the enzyme can be retained within the profile of the sensor device and, as it no longer needs to protrude beyond the surface of the sensor device, it is thereby rendered less susceptible to being removed by friction or abrasion during insertion into tissue.

20 Thus according to our invention we provide new sensor devices comprising an enzyme electrode sensor in which active electrode material carries an enzyme, characterised in that the enzyme is retained within one or more cavities formed in the said electrode sensor.

25 By placing the cavity (or cavities) along the length of the electrode core, the enzyme therein can face laterally instead of being on a mechanically vulnerable wire tip.

 The core of active electrode material may be made of any of the conventional conducting materials known for use
30 in the art of sensor electrodes. Preferably it is a noble metal, for example gold or platinum, or an alloy of these with each other or one or more other elements. Preferably the material is platinum itself, but as platinum itself is relatively soft it can be hardened by alloying with a
35 proportion of iridium.

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The shape of the sensor device is most conveniently of a substantially circular cross-section, as is customarily the case when the active electrode material is a wire core, e.g. conventional drawn metal wire as available commercially, but may be of any other cross-section if
5 desired. The size of the core material is preferably in the range 50 to 150 μm . though larger or smaller sizes may be used if desired. Our aim is to use as thin a core as can be found to be practical, consistent with the requirement that
10 its strength and integrity are not impaired by the size of the cavities.

As the purpose of the construction is for the sensor to present an enzyme-covered surface to its environment, it will normally be found that if any bare active electrode
15 material is also exposed to the environment it will interfere with the measurements made at the surface beneath the enzyme. A bare surface of active electrode material can be tolerated if such interference does not occur, but the preferred form is that in which a core of the active
20 electrode material is covered with a coating of insulating material to prevent bare active electrode material coming into contact with the environment media and the analyte to be detected and measured. Such an insulating material should be suitably durable, stable and resistant to the environment
25 media, effectively sealed over the core of active electrode material, and - when intended for use in vivo - be suitably bio-compatible and harmless in use. Such materials are well known in the art.

Consequently, when the sensor to be used has such a
30 coating of insulating material, the cavities required for our invention may be made in several ways. One way is for the insulation to be stripped off to expose a bare core of active electrode material and form the cavity into which the enzyme can then be placed. Alternatively, both the
35 insulation and some of the core of active electrode material

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can be removed by using an appropriate micro-machining technique, so that the insulation is removed and a cavity is also formed in the core of active electrode material itself. This latter procedure has the advantage that the fabrication is simplified and also that the cavities in the active electrode material allow for a greater surface area of the active electrode material to be exposed to enzyme and used to generate stronger signal outputs.

The cavities may be formed by conventional procedures, for example drilling, punching, grinding, boring, cutting, or any combination of these techniques, and the size and shape of the cavities may take any form which is considered most convenient and capable of retaining the desired enzyme in sufficient quantity. Likewise, the number of cavities may may be as large or small as desired, and will be determined to some degree by the size, shape and position of the cavities used in any particular instance. Our preference is for the cavities to be of a size up to about half of the overall thickness of the sensor material, so that the strength of the sensor is not unduly reduced. The optimum in any particular case may be readily determined by simple trial. The method used for forming the cavities may be a mechanical one, though that can be difficult on the micro-scale required; therefore we prefer to use an ion beam or laser method (commonly referred to a "micro-machining") as this is more easily used on the scale of size involved here. Thus a laser or ion beam can be used to etch, cut or bore into the material of the sensor to form the required cavities.

Examples of suitable shapes for the cavities include circular, oval, square, polygonal, cruciform, star-shaped and combinations of these. The cavities may regular or irregular in their, size, shape, number and distribution, though it is generally preferred (as being more convenient) to make all the cavities of substantially the same shape and

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size. It is preferred that the form of the cavities should be chosen so that they can readily retain the enzyme; thus dish-shaped cavities may be less efficient if the enzyme is not strongly held, and cavities which are more like "pits" are usually to be preferred as they achieve a stronger hold on their enzyme contents.

Another useful cavity shape is a slot cut into the sensor in a substantially lengthways direction (i.e. in the direction of the axis of a wire electrode), as this can minimise the number of cavities to be made. The size of the slot (length and breadth) may be varied to suit particular needs and usually are not critical.

An especially useful form of cavity is one which passes completely through the core of electrode material, in effect forming a tunnel, open at both ends, running transversely to the general direction of the inner core. This allows the enzyme to be packed into this tunnel and the enzyme contents to be exposed to analyte and (in the case of an oxidase) also oxygen, as needed for reaction - thus giving very effective enzymatic action and consequent measurement efficiency. If desired the cavity may contain more than one enzyme, e.g. as laminate layers, so that a succession of reactions can be catalysed --- one enzyme acting on an analyte substrate to form a product which, in turn, is acted upon by the second enzyme to generate a further product which can then be satisfactorily detected and measured at the active electrode surface.

The enzyme may be used in conventional formulations and compositions, and placed in the cavities and retained therein by conventional coating methods and fixing methods. For example the enzyme may be applied as a composition which coats and fills the cavities (e.g. by dipping) followed by wiping or passing through a collar to remove the surplus and especially any on the main surface where it is not required.

The enzyme can then be fixed in place by cross-linking, e.g.

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by treatment with glutaraldehyde.

The enzyme may be any of the conventional enzymes used in sensor enzyme electrodes for electrochemical analysis, but we find oxidase or dehydrogenase enzymes are most useful. An especially useful example is glucose oxidase, which allows the device to be used for detection and measurement of glucose concentrations in tissues. Though we describe our invention with particular reference to glucose and glucose oxidase, however, it is not limited to this specific system and it is applicable to other substrate/enzyme systems, of which several are well known in the art for analytical purposes.

The sensor devices of our invention preferably also comprise coatings over the enzymes held within the cavities. Thus, additional layers of material may be deposited over the enzyme after that has been put into the cavities. Such over-coating layers may be composed of materials of appropriate permeability (simple or selective) to regulate the passage of components from a sample under examination to the enzyme and active electrode surface, or excluding or limiting access by materials which could interfere with the measurements. These materials are well known in the art and are usually in a thin form which serves as a permselective membrane, and may be applied by conventional means also well known in the art.

Examples of such materials include various polymers and polymer compositions, e.g. polyaryl ether sulphones and modified polyurethanes.

The electrodes of this invention may be used by any of the conventional procedures well known in the art, but of all the electrochemical procedures available we prefer to use an amperometric procedure with the active electrode material as the anode.

The sensor devices of our invention can be used in vivo or in vitro, and the mode of insertion into the sites for

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making measurements are conventional. For in vivo sites, they may be inserted directly (transcutaneously into tissue) or through a cannula or even fine tubing. e.g. of nylon.

5 The advantages of the invention are especially in the way it provides new sensors which are small, light in weight, and potentially much more robust, flexible and suitable for implantation without attendant discomfort and other problems. Other advantages stem from the way in which the new sensors provide a different orientation and profile
10 for the sensing surfaces - side-oriented micro-machined sensing surfaces - to the samples under examination,

The invention is illustrated but not limited by the accompanying drawings, which illustrate some forms which the improved electrodes can take.

15 These drawings are schematic and not drawn to scale, but are intended to show the principal features - in some cases emphasised by being out of scale.

In the drawings Figures 1 to 4 represent, in perspective view, various forms of sensor electrode devices
20 of according to this invention and the type and disposition of cavities, and Figures 5 to 10 illustrate cross-sectional views through such sensor devices at the position at which the cavity is made.

In detail, all of Figures 1 to 4 show a thin platinum
25 wire covered with insulation (1), with the said insulation covering the end (2) as well as the main body (1). The end (3) is adapted for continuation on and connection to the electrical measuring system (not shown).

In Figure 1, which shows the simplest form of the
30 invention, the insulated wire (1) is pierced by a hole (4) to form a cavity (5) which is filled with an immobilised enzyme composition.

In Figure 2, there is shown a form in which the insulated wire (1) is pierced by a series of holes (6), each
35 forming cavities filled with immobilised enzyme as in Figure

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1. In Figure 3, there is shown a form in which the insulated wire (1) is pierced by a series of holes (7), each forming cavities filled with immobilised enzyme as in Figure 1 but of a shape different from those in Figure 2, i.e. cruciform instead of round.

In Figure 4, there is shown a form in which the insulated wire (1) is stripped of its insulation to form a slot (8) in the direction of the axis of the insulated wire (1), and the resulting slot is filled with immobilised enzyme; in this variant, the slot (8) has been made by cutting out the cover layer of insulation but without cutting into the core of platinum wire itself, but a further alternative (not shown) is that of cutting the slot into the core of platinum metal in addition to cutting away the outer layer of insulation.

All of Figures 5 to 10 illustrate cross-sectional views of alternative forms of the cavity through a thin platinum wire covered with insulation where the cavity is made.

In Figure 5, which shows the simplest form of the invention, the insulated wire comprises a core of thin platinum wire (1) covered by an outer layer of insulation (2) with a part of the insulation cut away to leave a cavity (3) filled with an immobilised enzyme composition.

In Figure 6, a cavity (3) has been bored through the inner platinum wire core, passing through it completely from one side to the other, and is filled with an immobilised enzyme composition. The enzyme-filled cavity (3) is coated at each end with a layer of a membrane coating (4) which acts to protect the enzyme and provide a chosen degree of selectivity or regulation of access of components of the surrounding medium to the enzyme.

In Figure 7, the cavity (3) has been bored through the inner platinum wire core, passing through it completely from one side to the other, and is filled with an immobilised enzyme composition as in Figure 6, except that two different

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enzyme compositions (3A) and (3B) are used to fill the cavity (3). The enzyme contents are coated at each end with a layer of a membrane coating (4) as in Figure 6.

5 In Figure 8, the arrangement is essentially the same as for Figure 5 except that the cavity (3) is bored through the outer insulation layer (2) and also into the inner platinum wire core to form an inner pit in the platinum. This form has the advantage of having a larger surface area of the platinum exposed to enzyme and this produces greater
10 response signals for measurement.

In Figure 9, the arrangement is essentially the same as for Figure 6 except that the cavity (3) bored through the outer insulation layer (2) and completely through the inner platinum wire core has not been given any coating (4), so
15 that the enzyme composition contents of the cavity (3) are exposed directly to the surrounding media.

In Figure 10, the construction is that of Figure 6 but shows - with added arrows (9) - indication of flows of fluid past the membrane-covered apertures in the insulation.
20 These flows may be fast or slow, large or small, and may be the same or different. One variant which is practicable is for the two flows (9A) and (9B) to be different -- with one (9A) being the sample medium, from which analyte components can diffuse in to the enzyme through the membrane, while the
25 other flow (9B) can provide similar access by diffusion for necessary substrates for the enzyme system. For example, (9A) may provide the main source of glucose to a glucose oxidase system while (9B) may provide more of the oxygen necessary for the enzyme to function.

30 To fabricate the devices illustrated, the insulated platinum wire may be etched to remove the insulation layer and expose the platinum within, and subsequent polymerisation or other conventional techniques may be used to deposit the enzyme on the platinum surface. Covering the
35 enzyme in the cavity can be achieved by conventional

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techniques, for example application from solution by dipping. The thickness of the coating may vary, but should be thin enough to allow adequate diffusion of a desired analyte without unduly impeding the ability of the material contacting the enzyme to change frequently enough to give a satisfactory overall view of the rate of changes there may be in the medium surrounding the sensor device.

The etching and boring operations indicated above were carried out using a copper laser.

The thin platinum wire used is a commercially available one, as commonly used for making wire electrodes, since it is not necessary to use a special wire. If the coating of insulation on commercially available wire is not suitable for use in any particular intended environment, the coating as supplied can if necessary be removed and replaced by re-coating with a more suitable insulation or a coating of the preferred insulation material may be deposited over the one already on the commercial wire.

The method of fabrication according to this invention, and illustrated herein, enables insulated monopolar platinum wire electrodes having an outer diameter of 50 to 150 μm and a series of laser-drilled transaxial cavities (which we refer to as fenestrations) each approximately 30 μm in diameter for wire-shaft enzyme loading to be made without undue difficulty.

Using laser-etching of an insulated platinum wire of 25 to 50 μm outer diameter to remove insulation locally allows further miniaturisation and can create an ultra-fine working electrode surface on which thin layers of enzyme and barrier films can be deposited.

These provide embodiments provide protection for the active enzyme and have unique device geometry; configurations as illustrated provide side-oriented enzyme surfaces in micro-machined sensing surfaces designed to retain and protect them.

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Construction as in Figure 6 in particular internalises the enzyme in the working electrode, giving a unique twin-surface enzyme with radial product diffusion into the surrounding platinum surface. The greater area of active platinum surface (i.e. surface exposed to the enzyme) can improve the efficiency with which the enzyme functions and so improve the measurements, for example in the linearity of response.

In use, the device can be inserted into tissue and, though the tip naturally must enter first, this entry does not damage the enzyme-containing areas of the surface. When the wire is pure platinum it may be too soft for direct insertion to be easy, so subcutaneous implantation of such "soft" wires will be through narrow bore nylon tubes. Alternatively, direct insertion can be made easier by using a platinum/iridium alloy wire, which is more rigid.

For determination of analytes, the procedures used were conventional ones and not described in detail here as they are well known in the art and do not involve any departures from the usual ones.

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WHAT WE CLAIM IS:-

1. A sensor device comprising an enzyme electrode sensor,
characterised in that the enzyme is retained within one or
5 more cavities formed in the said electrode sensor.
2. A sensor device as claimed in Claim 1 wherein the cavity
or cavities are placed along the length of the electrode
core, so that the enzyme therein can face laterally
instead of being on a mechanically vulnerable tip,
10 especially a wire tip.
3. A sensor device as claimed in Claim 1 or Claim 2 wherein
the core of active electrode material is made of a noble
metal, for example gold or platinum, or an alloy of these
with each other or one or more other elements, and
15 preferably of platinum itself or platinum hardened by
alloying, e.g. with a proportion of iridium.
4. A sensor device as claimed in any of Claims 1 to 3
wherein the shape of the sensor device is of a
substantially circular cross-section, for example as is
20 customary when the active electrode material is a wire
core, e.g. conventional drawn metal wire as available
commercially,
5. A sensor device as claimed in any of Claims 1 to 4
wherein the size of the core material is in the range 50
25 to 150 μm .
6. A sensor device as claimed in any of Claims 1 to 5
wherein the core of active electrode material is covered
with a coating of insulating material to prevent bare
active electrode material coming into contact with the
30 environment media and the analyte to be detected and
measured.
7. A sensor device as claimed in any of Claims 1 to 6
wherein the cavity or cavities required are made by
removing part of the insulation to expose a bare core of
35 active electrode material and the cavity (or cavities)

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form in the insulation layer and then the enzyme can then be placed therein.

- 5 8. A sensor device as claimed in any of Claims 1 to 7 wherein the cavity or cavities required are made by removing both the insulation and some of the core of active electrode material can be removed by using an appropriate micro-machining technique, so that the cavity (or cavities) form in the core of active electrode material itself.
- 10 9. A sensor device as claimed in any of Claims 1 to 8 wherein the one or more cavity is in the form of a slot cut into the sensor in a substantially lengthways direction (i.e. in the direction of the axis of a wire electrode),
- 15 10. A sensor device as claimed in any of Claims 1 to 9 wherein one or more cavity passes completely through the core of electrode material, in effect forming a tunnel, open at both ends, running transversely to the general direction of the inner core, so allowing enzyme to be packed into this tunnel and to be exposed to analyte-containing media at both ends of the cavity (tunnel).
- 20 11. A sensor device as claimed in any of Claims 1 to 10 wherein the cavity or cavities required are made by mechanical procedures, for example drilling, punching, grinding, boring, cutting, or any combination of these techniques,
- 25 12. A sensor device as claimed in any of Claims 1 to 11 wherein the cavity or cavities required are made by an ion beam or laser method (commonly referred to a "micro-machining").
- 30 13. A sensor device as claimed in any of Claims 1 to 12 wherein the size of the cavity (or cavities) is up to about half of the overall thickness of the sensor material, so that the strength of the sensor is not unduly reduced.
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14. A sensor device as claimed in any of Claims 1 to 13 wherein there are multiple cavities of substantially the same shape and size.

5 15. A sensor device as claimed in any of Claims 1 to 14 wherein the cavity form can readily retain the enzyme, preferably like "pits," which can achieve a stronger hold on their enzyme contents.

10 16. A sensor device as claimed in any of Claims 1 to 15 wherein the cavity (or cavities) contain more than one enzyme, e.g. as laminate layers, so that a succession of reactions can be catalysed --- one enzyme acting on an analyte substrate to form a product which, in turn, is acted upon by the second enzyme to generate a further product which can then be satisfactorily detected and
15 measured at the active electrode surface.

17. A sensor device as claimed in any of Claims 1 to 16 wherein the enzyme is fixed in place in the cavity (or cavities) by cross-linking, e.g. by treatment with glutaraldehyde.

20 18. A sensor device as claimed in any of Claims 1 to 17 having a coating over the enzyme held within the (or cavities) formed by depositing layers of material over it after enzyme has been put into the cavities

25 19. A sensor device as claimed in Claim 18 wherein the over-coating layer is composed of material of appropriate permeability (simple or selective) to regulate the passage of components from a sample under examination to the enzyme and active electrode surface, or excluding or limiting access by materials which could interfere with
30 the measurements.

20. A sensor device as claimed in any of Claims 1 to 19 wherein the enzyme is an oxidase or dehydrogenase enzyme, for example glucose oxidase.

35 21. A sensor device having one or more enzyme-containing cavities, substantially as described.

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22. Use of a sensor device as claimed in any of Claims 1 to 21 for the purpose of determining or monitoring an analyte.

5 23. Use of a sensor device, as claimed in Claim 22, wherein the analyte is glucose.

24. Use of a sensor device, as claimed in Claim 22 or Claim 23, in a biological environment or with biological media.

10 25. Method for analysis using a sensor device as claimed in any of Claims 1 to 21, especially electrolytic analysis and preferably using an amperometric procedure with the active electrode material as the anode.

15 26. Method as claimed in Claim 25 wherein the analysis is carried out in vivo, for example with the sensor device being inserted into the site for making measurements directly (transcutaneously into tissue) or through a cannula or fine tubing, e.g. of nylon.

27. Method for analysis using an enzyme-containing sensor device substantially as described.

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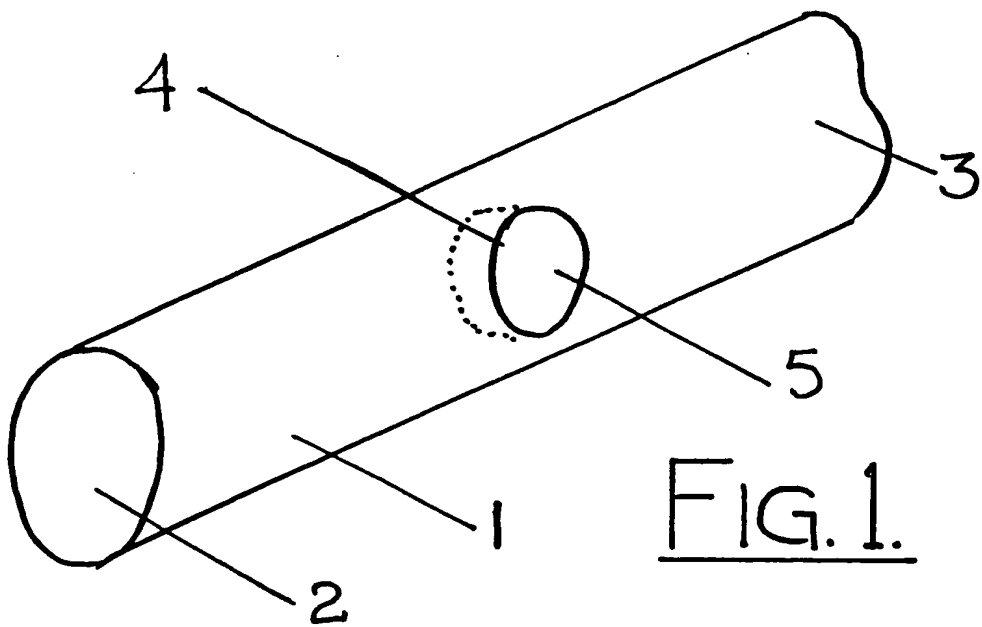


FIG. 1.

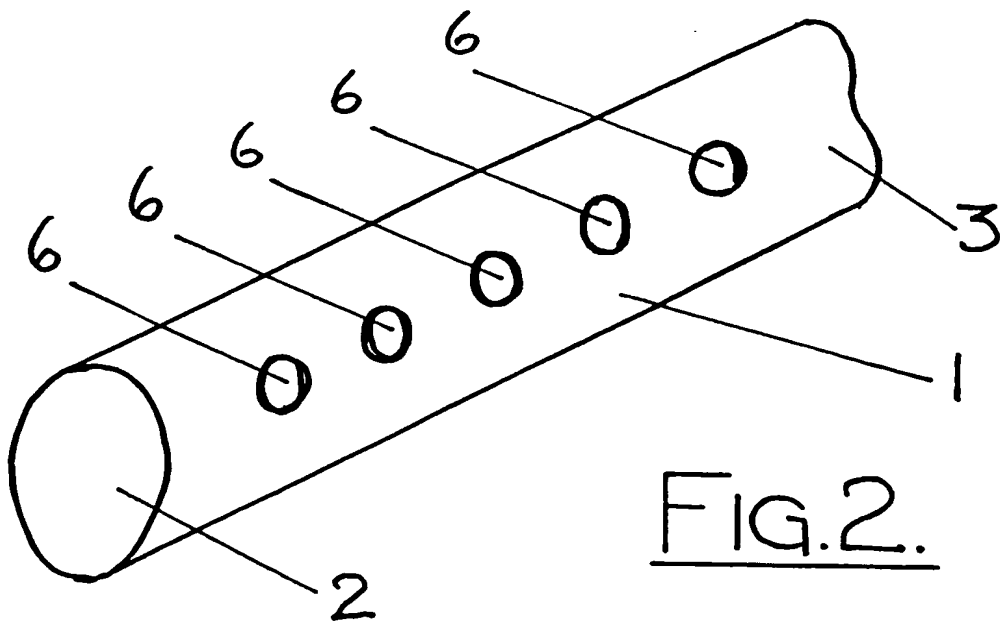
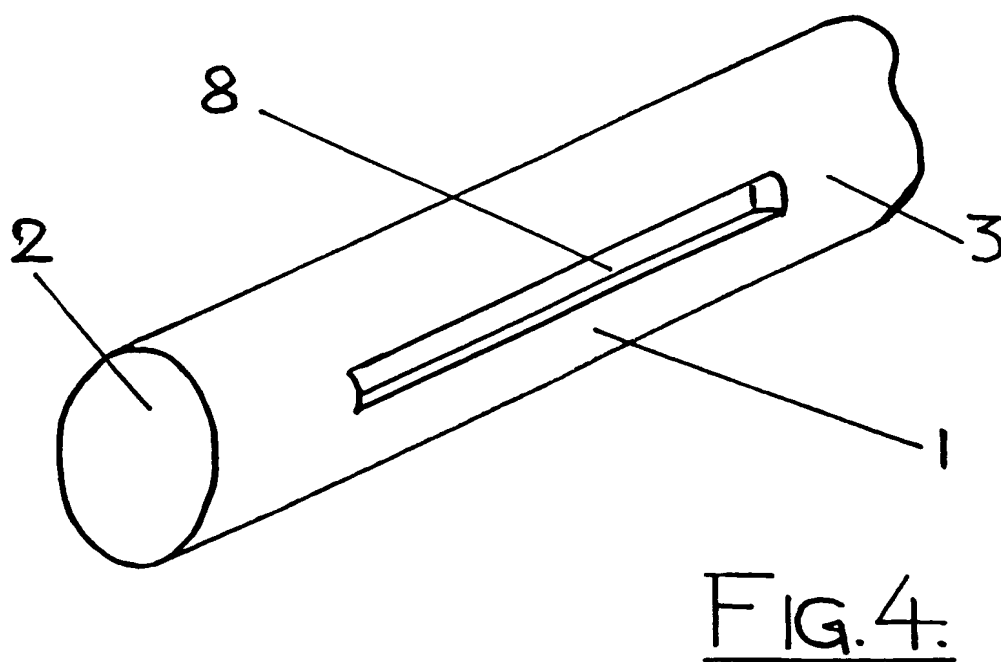
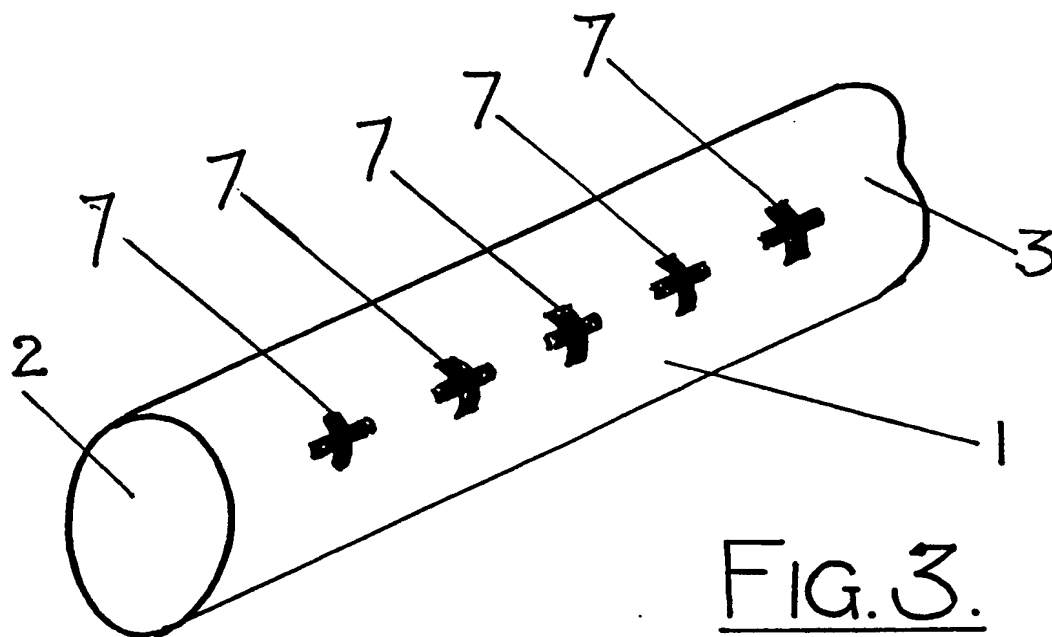


FIG. 2.

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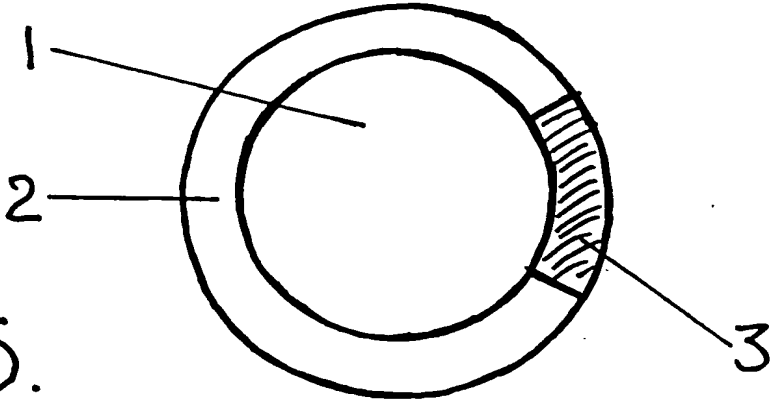


FIG. 5.

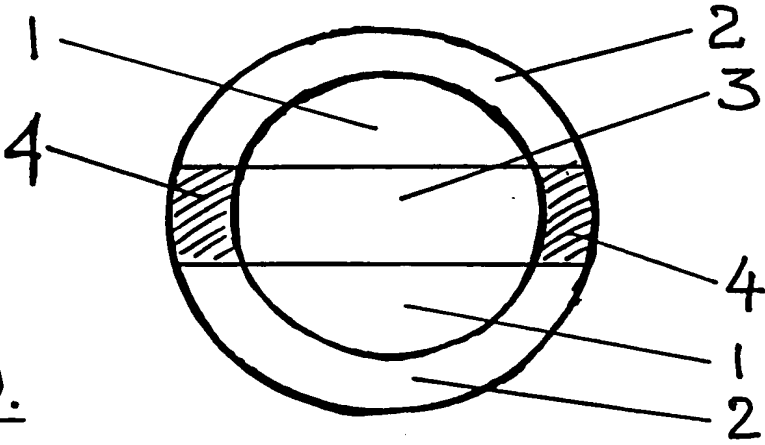


FIG. 6.

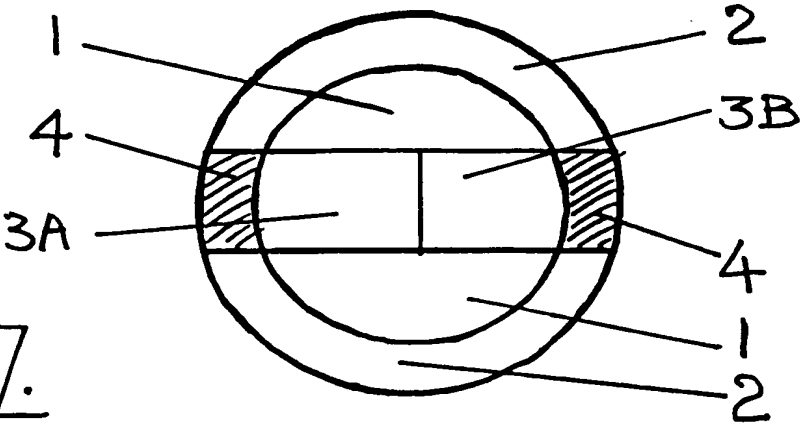


FIG. 7.

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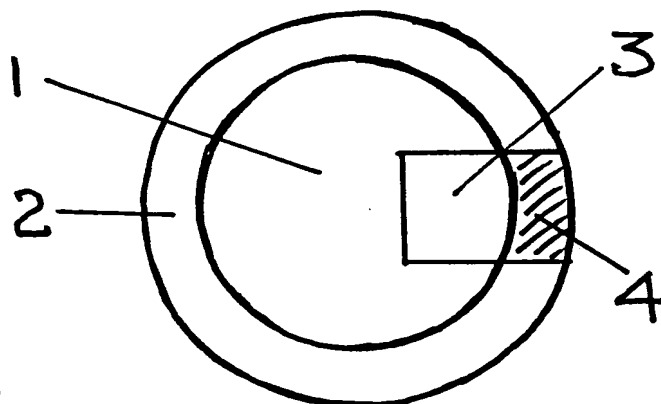


FIG. 8.

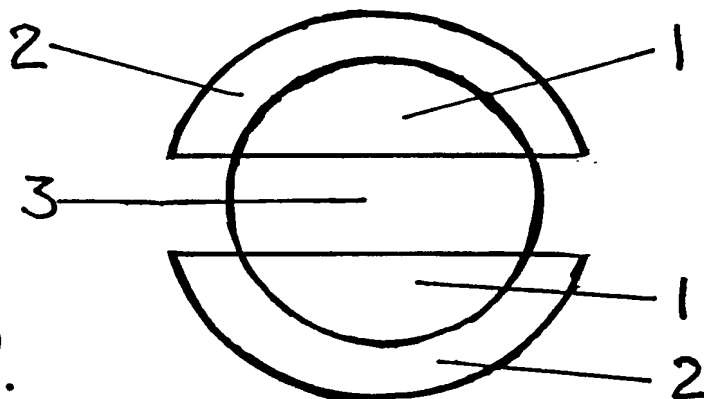


FIG. 9.

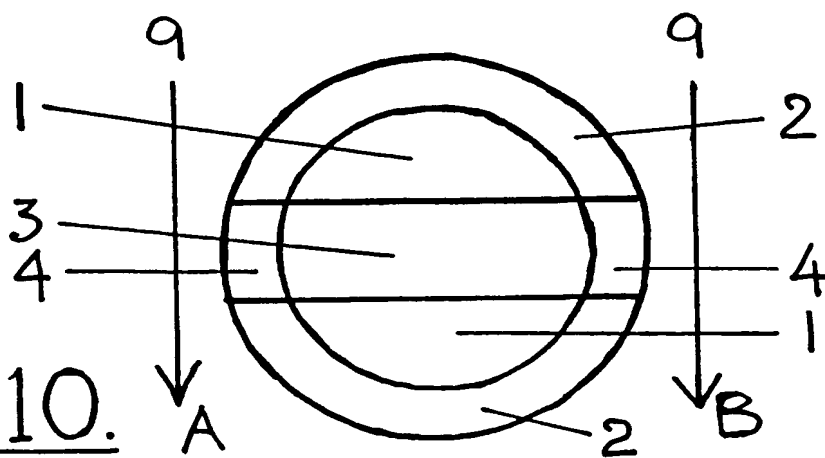


FIG. 10.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/03054

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 G01N27/327 A61B5/00 C12Q1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61B C12Q G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, COMPENDEX, INSPEC, EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 58250 A (ELAN CORP PLC) 23 December 1998 (1998-12-23) page 19, line 5 figures 2,3 ---	1-9, 11-27
X	WO 96 14026 A (KELLY JOHN GERARD ;ELAN MED TECH (IE); GROSS JOSEPH (IE)) 17 May 1996 (1996-05-17) page 39, line 17 -page 40, line 2 figures 16,17 ----	1-13, 15-27
X	US 5 660 163 A (LUCISANO JOSEPH Y ET AL) 26 August 1997 (1997-08-26) abstract column 5, line 55 - line 59 column 9, line 32 - line 39 figure 4 ----- -/-	1-9, 11-17, 20-27

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

3 November 2000

Date of mailing of the international search report

09/11/2000

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/03054

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